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Reappraisal of hemithyroidectomy and prophylactic lateral neck dissection for germline *RET* mutation-negative (true sporadic) medullary thyroid carcinomas

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Introduction

ATA guidelines recommend total thyroidectomy for medullary thyroid carcinoma (MTC) with or without *RET* mutations (1).

Since November 1995, our institution conducted preoperative germline *RET* gene mutation testing for all patients with MTC.

Miyauchi *et al*. reported that MTC without germline *RET* mutation did not present with multiple lesions in both lobes, and that hemithyroidectomy did not increase the risk of recurrence. Therefore, they recommended unilateral hemithyroidectomy for true sporadic MTC (2,3).

They also reported that prophylactic lateral lymph node dissection (p-LND) on the ipsilateral side contributed to biochemical cure and recommended p-LND on the ipsilateral side for patients without cN1b disease(2,3).

Therefore, for germline mutation-negative (true sporadic) MTC, we have performed hemithyroidectomy, central node dissection, and prophylactic/therapeutic lateral node dissection as a standard surgical method.

Aim

The aim of this study is to verify the validity our therapeutic strategy for true sporadic MTC.

Result

On preoperative imaging studies, only 3 patients (1.8%) showed multiple lesions in the thyroid , and all were located in one lobe (Table 1).

We generally performed hemithyroidectomy. However, 51 patients (31.3%) underwent total thyroidectomy because of physician's choice, coexisting thyroid autoimmune diseases and other lesions in contralateral lobe (Table 2), and none of these 51 were detected MTC lesions in contralateral lobe on postoperative pathological examination (Table 4).

None of the 112 patients who underwent hemithyroidectomy, showed recurrence to the remnant thyroid to date (Table 5).

Of the 122 cN0 MTC, 120 (98.4%) underwent not only central node dissection but also p-LND (Table 6,7).

Twenty-nine patients (24.2%) were pathologically diagnosed as pN1b, and 21 of these (72.4%) achieved biochemical cure (Table 7).

Result

To date, none of these 120 patients showed postoperative lymph node recurrence (Table5).

The prognosis of our series was excellent; 5-year recurrence-free survival (RFS) and cause-specific survival (CSS) rates were 92.9% and 98.7%, respectively and 10-year RFS and CSS rates were 89.6% and 97.9%, respectively (Figure 1, 2).

Conclusion

Our reappraisal suggests that hemithyroidectomy is appropriate for MTC confirmed as *RET* gene mutation-negative (true sporadic) before surgery, and that p-LND for cN0 MTCs >10 mm should contribute to high incidence of biochemical cure.

Patients & Methods

- We enrolled 163 sporadic MTC patients who underwent initial surgery between 1995 and 2022 in Kuma Hospital. Median postoperative follow-up period was 9.0 years (0.5-28.2 years).
- *RET* gene mutation analysis was performed for all patients and confirmed negative for *RET* mutation preoperatively.
- The extent of resection and lymph node dissection was confirmed in the operative record.
- The presence of multiple lesions for sporadic MTC was assessed by histopathology.
- Postoperative lymph node, remnant thyroid and distant recurrence were confirmed from the medical record.
- Within one month after surgery, a calcium loading test was performed and calcitonin levels were measured to determine biochemical cure.
- We assessed the frequency of pN1b and biochemical cure in cN0 cases who underwent p-LND.
- Kaplan-Meier method was adopted to analyze the recurrence free survival (RFS) and cause-specific survival (CSS) for sporadic MTC.

Table 1. Backgrounds and clinical features of the patients in sporadic MTC

Variables		Sporadic MTC (N=163)
Gender	Male	49 (30.1%)
	Female	114 (69.9%)
Age at operation	Median (Range min-max)	59 (17-80)
Multiplicity at diagnosis	Yes*	3 (1.8%)
Tumor size at the MTC diagnosis(mm)	Median (Range min-max)	18.0 (0.0-133.3)
cN	0	122 (74.8%)
	1a	5 (3.1%)
	1b	36 (22.1%)
cM	Yes	1 (0.6%)

* all were located in one lobe

Table 2. Extent of thyroid resection and reason

		Sporadic MTC (N=163)
Thyroidectomy		
	total or near-total	36 (22.1%)
	Subtotal	15 (9.2%)
	hemithyroidectomy	112 (68.7%)
Reason for more than hemithyroidectomy		N=51
	physician's choice*	17(33.3%)
	coexisting thyroid autoimmune diseases**	5 (9.8%)
	other lesions in contralateral lobe***	29(56.9%)

* Reason for large tumor, bilateral lymph node metastases, and suspicious for multiple MTC
** 3 cases were Graves' disease, 2 cases were chronic thyroid disease
*** 7 cases were TPC, 18 cases were adenomatous nodule and 4 cases were follicular neoplasm

Table 3. lateral lymph node dissection

		Sporadic MTC (N=163)
prophylactic LND*	yes	125 (76.7%)
therapeutic LND	yes	36 (22.1%)
Central only	yes	2**(1.2%)

*LND: lateral lymph node dissection
** Two cases were microcarcinoma (≤10mm)

Table 4. pathological features, biochemical cure and postoperative complications of the patients in sporadic MTC

Variables		Sporadic MTC (N=163)
multiplicity*	Yes	0
intrathyroidal metastasis**	Yes	44 (27.0%)
pN	0	84 (51.5%)
	1a	11 (6.7%)
	1b	68 (41.7%)
Ki67 LI***	<5%	140 (93.3%)
	≧5%	10 (6.7%)
Biochemical cure	Yes	118 (72.4%)
Permanent hypothyroidism	yes	68 (41.7%)
Permanent hypoparathyroidism	yes	1 (0.6%)

* Among 51 cases of near-total thyroidectomy or more extensive surgery, no instances of contralateral MTC were observed.
** Three cases that were diagnosed as multifocal MTC preoperatively were diagnosed as intrathyroidal metastasis in the postoperative pathology.
*** LI: labeling index

Table 5. initial recurrence sites in 16 patients* (9.9%)

1. Lymph node	13*(8.0%)
2. Remnant thyroid	0
3. Distant organs	3*(2.5%)

* None of the patients who underwent cN0 p-LND had post-operative lymph node recurrence.

Table 6. pN1b rate at cN

		cN0	cN1a	cN1b	p-value＊
pN1b	positive	**29 (23.8)**	**5 (100.0)**	36 (100.0)	<0.001
	negative	93 (76.2)	0 (0.0)	0 (0.0)	

* Kruskal-Wallis test

Table 7. Biochemical cure rate at cN0 (N=122)

p-LND*		Performed (N=120)		Not preformed (N=2)**
pN1b		Positive (N=29)	Negative (N=91)	
Biochemical cure	yes	**21 (72.4)**	79 (86.8)	2 (100.0)
	no	8 (27.6)	12 (13.2)	0 (0.0)

* p-LND: Prophylactic lateral lymph node dissection
** Two cases were microcarcinoma (≤10mm)

Fig.1 RFS for sporadic MTC

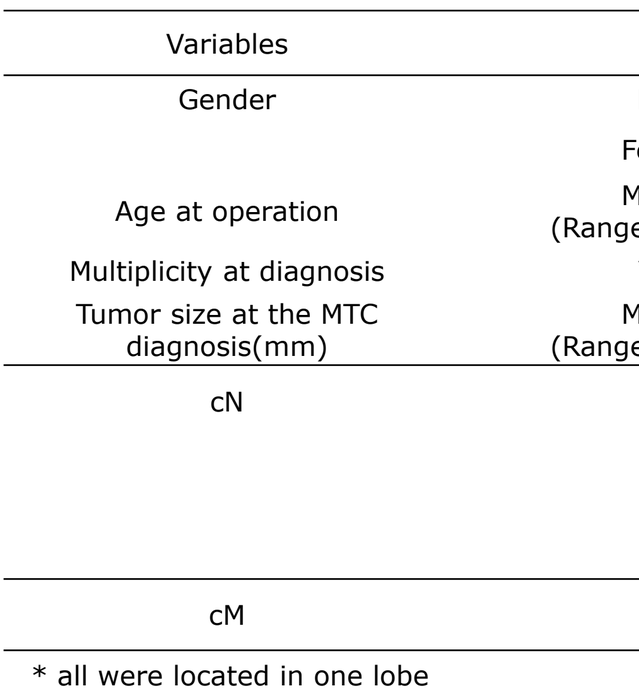
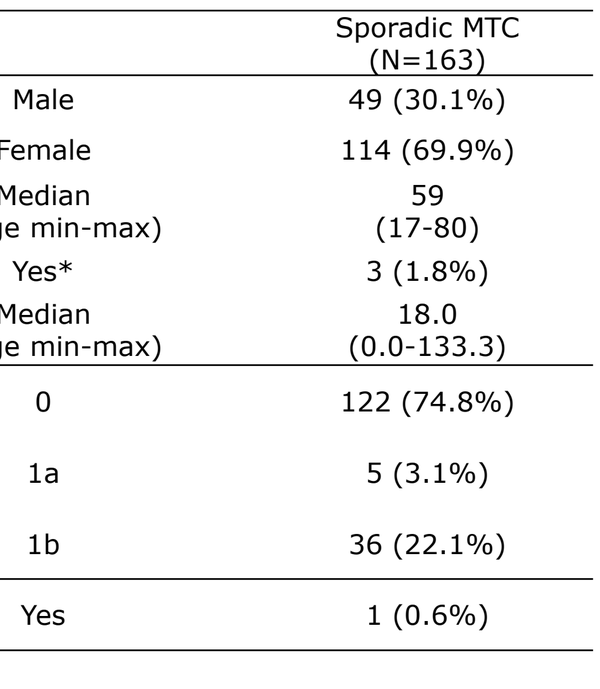


Fig.2 CSS for sporadic MTC



References

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